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ORIGINAL ARTICLE

Epidemiology of Allergic Disease

Dietary patterns and respiratory health in adults from nine European countries—Evidence from the GA^{2}LEN study

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Summary

Background: Dietary patterns defined using principal component analysis (PCA) offer an alternative to the analysis of individual foods and nutrients and have been linked with asthma and allergic disease. However, results have not been reproducible in different settings.

Objective: To identify dietary patterns common to different European countries and examine their associations with asthma and allergic symptoms.

Methods: In sixteen study centers in nine European countries, 3206 individuals aged 15-77 years completed a common, internationally validated, food frequency questionnaire and a respiratory symptoms questionnaire. The outcomes of interest were current asthma, asthma symptoms score (derived based on responses to 5 asthma symptom-related questions), atopy (positive skin prick test). Spirometry was used to estimate forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), the FEV_1/FVC, spirometric restriction (FVC below the lower limit of normal (<LLN)) and FEV_1/FVC < LLN. A novel meta-analytic approach was used to identify dietary patterns using PCA and to examine associations with asthma and allergic symptoms.

Results: Two dietary patterns emerged, generally correlating with the same foods in different countries: one associated with intake of animal proteins and carbohydrates; the other with fruit and vegetables. There was evidence that the former pattern was associated with a higher asthma score (RR 1.63, 95% CI: 1.33-2.01), current asthma (RR 2.03, 95% CI: 1.52-2.71), wheeze (RR 1.84, 95% CI: 1.30-2.60), atopic status (RR 1.68, 95% CI: 1.16-2.44) and with decreased lung function, including an FVC <LLN (RR 4.57, 95% CI: 2.27-9.21).

Conclusions and Clinical Relevance: Our findings suggest an increase in sensitisation to common allergens, an increase in asthma symptoms, and a reduction in lung function in those eating a diet rich in animal proteins and carbohydrates. We found little evidence of an association between these outcomes and eating a diet rich in fruits and vegetables.

KEYWORDS

asthma, dietary patterns, meta-regression, nutritional epidemiology, principal components analysis

1 | INTRODUCTION

There is accumulating evidence from observational studies that high intakes of fruit and vegetables have a protective effect in children and adults with asthma.[1] Additionally, asthma has been associated with low intakes of dietary antioxidants and particularly with vitamins C, D and E and selenium.[2-4] However, trials of supplementation have been unsuccessful and have contradicted the findings from observational studies.[5-7] This may be because apparent effects in the observational studies were confounded by lifestyle factors or by other dietary components.[8,9]

In the last decade, the use of principal component analysis (PCA) has offered an alternative to analyzing dietary exposures as single foods or nutrients, by empirically identifying consistent dietary patterns. Observational studies in adults from Europe have shown a positive association between dietary patterns that reflect a more 'Western diet' and asthma risk[10-13] and have been associated with lower ventilatory function.[14] On the other hand, having a 'prudent' pattern, usually characterized by fruit and vegetable intake, has been associated with lower risk of chronic obstructive pulmonary disease (COPD)[15,16] and better ventilatory function.[13,14] However, other population-based studies have not confirmed these associations when linking PCA-derived dietary patterns to asthma,[17] ventilatory function,[18] or allergy-related outcomes.[17,19] A possible reason for the contradictory findings is that results from dietary patterns derived with the use of PCA have not always been reproducible across different settings.[20]

In order to address this limitation of PCA, we used a novel approach for the analysis of food frequency questionnaire (FFQ) data across different countries, a meta-analytic approach to PCA (meta-PCA).[19] Our aim is to explore associations between dietary intake and respiratory and allergic symptoms in European populations participating in the Global Asthma and Allergy Network of Excellence (GA^2LEN) study.

2 | METHODS

2.1 | Study design and population

GA^2LEN was a European Union-funded Network of Excellence which coordinated a study of genetic and environmental risk factors for allergy and asthma in adult and adolescent populations across 18 participating centers in 11 European countries. In brief, the GA^2LEN follow-up survey is a cross-sectional study among those previously contacted in baseline postal surveys of representative adult populations who were willing to be contacted again. Three groups of cases (those with asthma, those with sinusitis, and those with both asthma and sinusitis) and one group of controls (those with neither asthma nor sinusitis) were drawn from the postal survey sample and invited for follow-up. Administered questionnaires were used to obtain information on age, gender, smoking, and various environmental factors and the presence of symptoms of asthma, chronic rhinosinusitis, and allergic rhinitis. As part of the GA^2LEN Follow-up Survey, we established the GA^2LEN Dietary Study, where dietary intake was enquired using a self-completed FFQ ('dietary intake in adults from the GA^2LEN Follow-up Survey ClinicalTrials.gov Identifier: NCT03251157). Clinical assessment was also done and included measurement of height, weight, allergen skin prick test (SPT), blood samples for total and specific immunoglobulin E (IgE) and lung function. Detailed description of the study is provided elsewhere.[21]

2.2 | Respiratory and allergic outcomes

A continuous measure of asthma symptoms (asthma score) was derived.[22] It is the sum of positive responses to questions regarding the following symptoms in the last 12 months: wheeze with breathlessness, chest tightness, attack of shortness of breath (SOB) coming on at rest, SOB after exercise, and being woken by SOB. The score ranged from 0 (no symptoms) to 5 (having all the symptoms enquired). Asthma was also defined as present in those who had answered yes to having a diagnosis of asthma and either wheezing, waking up with chest tightness, waking up with shortness of breath, or waking at night with an attack of coughing in the previous 12 months. Other respiratory symptoms included allergic rhinitis, which was defined as a positive response to the question “Do you have any nasal allergies including hay fever?”, and eczema was defined as a positive response to the question “Did you ever have eczema or any kind of skin allergy?”.

Skin prick tests (SPTs) to grass pollen, grass mix, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cockroach (Blatella), olive, Alternaria, dog, Artemisia, birch, cat, and Parietaria were conducted. All tests with an average diameter ≥3 mm greater than control were taken to be positive (ie, histamine ≥3 mm and negative control <3 mm). Atopy was defined as any positive response to any of the allergens tested.

Spirometric lung function (forced expiratory volume in 1-second (FEV_1) and forced vital capacity (FVC)) was measured pre- and post-administration of bronchodilator (salbutamol 200 mg). Spirometric restriction was defined by an FVC below the lower limit of normal (<LLN), and chronic obstruction by an FEV1/FVC <LLN, defined according to the National Health and Nutrition Examination Survey (NHANES) III norms for Caucasians. All spirometries were checked centrally for quality. Only spirometry that met the ERS/ATS criteria was accepted.[23]

In all centers permission to conduct this study was obtained from appropriate local ethics committees, and all participants signed a written consent form after being fully informed about the study.

2.3 | Food frequency questionnaire (FFQ)

One GA^{2}LEN survey objective was to assess dietary intake across European countries using a single and standardized instrument that is common to all participant countries. The questionnaire included a set of 32 food sections and 239 food items. The FFQ sections were designed following the recommendations by the EFCOSUM Group,[24] which facilitate international comparisons of dietary intake. It also included several staple foods to capture locally representative dietary intake.

The FFQ enquired about intake of foods consumed over a period of 12 months to capture dietary habits during season. Participants reported how often they had consumed the foods over the previous month, using eight predefined options (rarely or never, 1-3 times/mo, once, 2-4, or 5-6 times/wk, once, 2-3 times/d). Standard food portion sizes were used to quantify the intake following the recommendations from the UK's Food Standards Agency. We estimated weekly intake (g) of foods and food groups by multiplying frequency of consumption by the weight of standard portion sizes. Macronutrient intakes and total energy intake (TEI) were derived using the latest available edition of McCance & Widdowson's Food Composition Tables.[25]

Respondents sometimes left individual items blank on the FFQs. This was assumed to denote zero intakes of these foods unless more than 20% of items were blank, in which case the FFQ was considered incomplete, and the subject was excluded from analyses. Participants were also excluded if they had extreme values of total energy intake, which might suggest an unrealistic response. We calculated the expected basal metabolic rate (BMR) with the given age, weight, and sex and excluded subjects with a ratio of energy intake to expected BMR that was either below the 0.05th sample centile or above the 99.5th sample centile for their country.

We have included in our analysis only food items which were consumed at least 1-3 times/wk by more than 5% of the individuals in our final sample.

The GA^{2}LEN FFQ was validated in five EU countries, namely Finland, Portugal, Germany, Poland, and Greece) and demonstrated to be a good tool to assess midterm intake of foods, specifically essential polyunsaturated fatty acids (PUFAs).[21] The instrument has also been demonstrated to be an accurate tool to assess dietary sources of flavonoids.[26]

2.4 | Statistical analyses

2.4.1 | Dietary pattern analyses with the use of meta-PCA

We derived dietary patterns using a meta-analytic method proposed by Hedges & Olkin.[27] This analysis was restricted to control participants in order to reflect diet in a healthy population. In each country we evaluated a Pearson product moment correlation, r, for each pair of food items. Each correlation coefficient was then transformed using a Fisher transformation

$$z = 0.5\log\left((1+r)/(1-r)\right)$$

to give it an approximately normal distribution with variance 1/(n-3), where n is the sample size for the country in question. For each pair of food items, a weighted average of these z-values over all countries was calculated, using the inverse variance (n - 3) as a weighting, and an inverse Fisher transformation was then applied to give a pooled correlation coefficient. A more detailed description of the method is provided in the technical note of the Data S1. Finally, PCA was applied to the matrix of pooled correlation coefficients, giving us dietary pattern scores (linear combinations of standardized food intakes) which could be used in all countries. A varimax rotation was applied to improve the interpretability of the patterns obtained, and the number of patterns extracted was chosen based on interpretability and an examination of the scree plot. This meta-analytic approach to PCA (meta-PCA) has previously been applied in the field of psychiatry,[28,29] and we have used it previously in dietary analysis.[19]

2.4.2 | Asthma and allergic symptoms

Within each country we used Poisson regression models with a robust error variance and linear regression models to investigate associations between dietary patterns (categorized in quintile groups)

TABLE 1 General characteristics of the study population # (based on individuals with complete data on dietary exposures and asthma score)

Variables	Countries: Denmark Odense (359)	Finland Helsinki (160)	Sweden Total (1261)	UK Total (173)	Germany (Duisburg) (200)	Germany Brandenburg (178)
Asthma score; N (%)						
0	145 (40.4)	96 (59.6)	583 (46.2)	66 (38.2)	74 (37.0)	87 (48.8)
1	85 (23.7)	31 (19.3)	276 (21.9)	37 (21.4)	62 (31.0)	45 (25.2)
2	50 (13.9)	15 (9.3)	195 (15.5)	22 (12.7)	26 (13.0)	21 (11.8)
3	47 (13.1)	10 (6.2)	114 (9.0)	17 (11.5)	18 (9.0)	17 (9.5)
4	24 (6.7)	7 (4.4)	61 (4.8)	26 (15.0)	10 (5.0)	6 (3.3)
5	8 (2.2)	2 (1.2)	33 (2.6)	5 (2.9)	10 (5.0)	2 (1.2)
Age, years; mean (SD)	48.1 (14.5)	46.8 (15.1)	45.7 (15.1)	51.6 (13.2)	49.0 (15.7)	49.8 (15.3)
Males, n (%)	162 (45.1)	62 (38.8)	556 (44.1)	70 (40.5)	85 (42.7)	67 (37.6)
BMI (m^2/kg)	27.4 (14.8)	26.5 (4.6)	25.9 (7.2)	27.1 (5.6)	27.2 (5.1)	26.7 (4.8)
Age at completing full-time education; years (SD)	23.4 (5.5)	23.5 (5.5)	24.5 (7.7)	18.1 (3.6)	20.2 (4.1)	20.7 (4.7)
Employment status						
Employed	188 (52.7)	94 (58.9)	737 (58.5)	85 (49.7)	102 (51.2)	94 (52.8)
Retired	82 (23.0)	32 (20.0)	199 (15.8)	39 (22.8)	44 (22.1)	44 (24.7)
Unemployed	11 (3.1)	3 (1.9)	38 (3.0)	4 (2.3)	7 (3.5)	5 (2.8)
Other	76 (21.5)	31 (19.4)	286 (22.7)	43 (25.1)	47 (23.8)	35(19.7)
Smoking						
Never smokers	155 (43.4)	83 (51.9)	672 (53.3)	77 (44.5)	92 (46.0)	91 (51.1)
Ex-smokers	102 (28.6)	37 (23.1)	428 (33.9)	70 (40.5)	75 (37.5)	56 (31.4)
Current smokers	100 (28.0)	40 (25.0)	162 (12.8)	26 (15.0)	33 (16.5)	31 (17.4)
Total energy intake (TEI)	2577 (761)	3197 (1140)	3110 (978)	2833 (889.6)	2906 (1106)	2734 (987)
Use of nutritional supplements, n (%)	143 (40.4)	70 (43.5)	325 (26.0)	58 (33.7)	53 (26.6)	49 (27.5)
% people eating fruits (all types) ≥5 times/wk	202 (56.4)	93 (57.1)	717 (56.0)	101 (57.7)	54 (48.2)	60 (54.5)
% people eating total vegetables (all types) ≥5 times/wk	224 (62.4)	128 (78.5)	906 (70.7)	92 (52.6)	104 (55.7)	90 (57.8)

Variables	Countries: Portugal Coimbra (270)	Belgium Ghent (148)	Poland Total (244)	The Netherlands Amsterdam (215)	Total 3206
Asthma score					
0	109 (41.0)	57 (38.5)	78 (32.0)	100 (41.0)	1395 (43.5)
1	49 (18.4)	34 (23.0)	73 (29.9)	40 (18.6)	732 (22.8)
2	41 (15.4)	22 (14.9)	34 (13.9)	37 (17.2)	463 (14.4)
3	27 910.2)	17 (11.5)	28 (11.5)	23 (10.7)	318 (9.9)
4	23 (8.7)	12 (8.1)	17 (7.0)	12 (5.6)	198 (6.2)
5	20 (6.4)	6 (4.1)	14 (5.7)	3 (1.4)	100 (3.1)
Age, years; mean (SD)	47.1 (15.0)	45.7 (15.1)	49.7 (15.7)	52.6 (13.9)	47.6 (15.1)
Males, n (%)	93 (35.0)	71 (48.0)	104 (42.6)	111 (51.6)	1381 (43.1)
BMI, m^2/kg (SD)	25.9 (5.1)	24.9 (4.4)	27.4 (5.2)	25.7 (3.7)	26.3 (5.2)
Age at completing full-time education; years (SD)	20.1 (4.6)	20.6 (6.6)	20.4 (3.4)	20.2 (4.6)	22.4 (6.6)
Employment status					
Employed	140 (52.6)	75 (51.0)	89 (38.0)	103 (47.9)	1707 (53.6)
Retired	56 (26.5)	26 (17.7)	86 (36.8)	56 (21.1)	664 (20.8)
Unemployed	11 (4.1)	3 (2.0)	12 (5.1)	5 (2.3)	99 (3.1)
Other	59 (22.2)	30 (22.4)	47 (20.0)	51 (23.7)	717 (22.5)

(Continues)

TABLE 1 (Continued)

Variables	Countries: Portugal Coimbra (270)	Belgium Ghent (148)	Poland Total (244)	The Netherlands Amsterdam (215)	Total 3206
Smoking					
Never smokers	172 (64.7)	75 (50.7)	111 (45.7)	84 (39.1)	1612 (50.4)
Ex-smokers	56 (21.1)	45 (30.4)	78 (32.1)	88 (40.9)	1035 (32.2)
Current smokers	38 (14.3)	28 (18.9)	54 (22.2)	43 (20.0)	555 (17.3)
Total energy intake (TEI); mean (SD)	3195 (1296)	2937 (885)	3211 (1661)	2817 (827)	2993 (1072)
Use of nutritional supplements, n (%)	16 (6.0)	50 (33.8)	53 (22.0)	88 (41.0)	905 (28.4)
% people eating fruits (all types) ≥5 times/wk	189 (70.8)	80 (54.1)	158 (64.0)	114 (52.3)	1867 (57.6)
% people eating total vegetables (all types) ≥5 times/wk	206 (77.2)	77 (52.0)	182 (73.7)	78 (35.8)	2087 (64.4)

TABLE 2 Associations of selected respiratory and allergic outcomes in relation to dietary patterns adjusted for potential confounders*

	"Fruit and vegetables diet"					"Animal proteins and carbohydrates diet"				
	Mean difference	95% CI	*P*-value	I^2 (%)	*P*-value for heterogeneity	Mean difference*	95% CI	*P*-value	I^2 (%)	*P*-value for heterogeneity
Total IgE (kU/L)	0.19	−0.09, 0.48	0.186	23.1	0.231	0.21	−0.06, 0.48	0.131	0	0.737
Questionnaire variables	**RR**	**95% CI**	***P*-value**	**I^2 (%)**	***P*-value for heterogeneity**	**RR**	**95% CI**	***P*-value**	**I^2**	***P*-value for heterogeneity**
Asthma score	1.18	0.88, 1.57	0.266	50.5	0.033	**1.63**	**1.33, 2.01**	**<0.001**	0	0.899
Self-reported asthma in the last 12 mo	0.99	0.75, 1.30	0.925	0	0.529	**2.03**	**1.52, 2.71**	**<0.001**	0	0.462
Doctor-diagnosed asthma	0.99	0.67, 1.47	0.963	35.4	0.124	**1.71**	**1.22, 2.38**	**<0.001**	0	0.713
Ever had asthma	1.03	0.75, 1.41	0.844	7.6	0.372	**1.61**	**1.17, 2.22**	**<0.001**	0	0.719
Wheeze in the last 12 mo	1.1	0.82, 1.47	0.538	27.5	0.19	**1.84**	**1.30, 2.60**	**<0.001**	32.4	0.149
Eczema in the last 12 mo	1.02	0.86, 1.22	0.789	18.3	0.274	1.1	0.92, 1.32	0.308	15.4	0.301
Allergic rhinitis	0.85	0.61, 1.18	0.329	52	0.027	1.12	0.85, 1.47	0.423	19.6	0.262
Positive skin prick tests										
Any of 11 inhalant and food allergens†	0.97	0.78, 1.20	0.779	29.5	0.173	1.68	1.16, 2.44	0.006	0	0.947
House dust mite (HDM)	1.08	0.76, 1.52	0.673	16.2	0.294	**1.39**	**1.00, 2.01**	**0.051**	0	0.768
Cat dander	1.29	0.82, 2.01	0.266	37.6	0.108	1.5	0.88, 2.57	0.137	47.5	0.046
Cockroach	1.2	0.77, 1.85	0.427	34.4	0.132	1.05	0.57, 1.93	0.873	56.7	0.013
Grass mix	0.93	0.64, 1.34	0.69	38.4	0.102	1.2	0.83, 1.73	0.337	33.0	0.144
Rye grass	1.02	0.76, 1.37	0.902	11.8	0.333	1.07	0.78, 1.45	0.681	7.9	0.369

Results of meta-analyses of the effect of principal component scores on respiratory and allergic outcomes. Mean difference, relative risks (RRs), and 95% confidence intervals (95% CI) represent increase in risk per quintile of dietary pattern scores. N = 3206. Bold values indicate *P*-value <0.01.

*All results presented are adjusted for age, sex, smoking status (never, ex-smoker, current), body mass index, age at completion of full-time education, occupation, use of nutritional supplements, and total energy intake (TEI).

†Grass pollen, grass mix, Dermatophagoides pteronyssinus, Dermatophagoides farinae, cockroach (Blatella), olive, Alternaria, dog, Artemisia, birch, cat, and Parietaria.

and respiratory and allergic outcomes. Regression results were pooled across countries using random effects meta-analysis, and heterogeneity was summarized using the I^2 statistic.[30]

2.4.3 | Confounders

All analyses were adjusted for the following potential confounders identified a priori: age, sex, smoking status (never, ex-smoker, current), body mass index (BMI), age at completion of full-time education, occupation, use of nutritional supplements, dietary patterns, and total energy intake (TEI). Further adjustment for weight and height was included when association between dietary intake and lung function measurements was examined. Sampling probability weights for each subject in each subset of the survey data were computed by dividing the frequency of the subject's center and case status in the postal survey by the frequency of this center and case status in the analysis dataset.

Statistical analyses were conducted using Stata 14.1 (Stata Corporation, College Station, Texas USA).

3 | RESULTS

Centers in Palermo (Italy) and Skopje (Macedonia) were excluded because of the small number of cases and additionally small number of individuals who completed the FFQ (n = 32 and n = 26, respectively). We analyzed the two German centers (Brandenburg and Duisburg) as if they were from different countries because of socioeconomic and demographic differences between their populations. Our final sample included 3206 individuals living in 16 centers in 9 countries with full data on FFQ data and confounders. Forty-three food items were excluded from our analysis due to infrequent consumption, leaving 196 out of the original 239 items. In total, 120 subjects were excluded from the study due to incomplete or implausible total energy intake. We compared the characteristics of those included (n = 3206) and excluded (n = 120) from the study, and both samples were very similar in terms of age, sex, BMI, education, employment, and smoking. Further descriptive data on health outcomes and confounders are presented in Table 1.

3.1 | Dietary patterns identified with the use of meta-PCA

We extracted two dietary patterns, which explained 16.8% of the variance in the original 196 items. A component score was created for each individual for each of the principal components identified. Table S1 (see Data S1) presents individual food items that correlated ≥0.3 or ≤–0.3 with the varimax rotated dietary patterns (principal components) in more than five different countries. According to Table S1 (see Data S1), in more than five countries the first pattern was characterized by high consumption of fruits and vegetables and the second one was closely associated with intakes of animal proteins and carbohydrates, and thus patterns were labeled accordingly.

3.2 | Asthma and allergic symptoms

There was evidence of an association of the animal proteins and carbohydrates pattern with asthma score (RR 1.63 per quintile, 95% CI: 1.33-2.01), self-reported asthma in the last 12 months (RR 2.03 per quintile, 95% CI: 1.52-2.71), doctor-diagnosed asthma (RR 1.71 per quintile, 95% CI: 1.22-2.38), ever had asthma (RR 1.61 per quintile, 95% CI: 1.17-2.22), wheeze in the last 12 months (RR 1.84 per quintile, 95% CI: 1.30-2.60), positive skin prick test to house dust mite (RR 1.39 per quintile; 95% CI: 1.00-2.01), and positive skin prick test to at least one of the 11 allergens (RR 1.68 per quintile; 95% CI:

TABLE 3 Associations of selected lung function outcomes in relation to dietary patterns adjusted for potential confounders*

	Fruit and vegetables diet					Animal proteins and carbohydrates diet				
Ventilatory function (post-bronchodilator measures)	**RR**	**95% CI**	***P*-value**	**I^2 (%)**	***P*-value of heterogeneity**	**RR**	**95% CI**	***P*-value**	**I^2 (%)**	***P*-value of heterogeneity**
FVC below the limit of normal	0.69	0.27, 1.70	0.421	69.3	0.001	**4.58**	**2.28, 9.22**	**0.001**	**50.9**	**0.031**
FEV1/FVC below the limit of normal	0.47	0.10, 2.26	0.352	79.7%	<0.001	1.63	0.81, 3.28	0.163	8.0%	0.447
	Mean difference	**95% CI**	***P*-value**	**I^2 (%)**	***P*-value of heterogeneity**	**Mean difference**	**95% CI**	***P*-value**	**I^2 (%)**	***P*-value of heterogeneity**
Spirometry										
log (FEV1 pre-bronchodilator (L))	0.04	−0.01, 0.08	0.112	53.5	0.022	**−0.07**	**−0.11, −0.03**	**<0.001**	12.4	0.329
log (FEV1 post-bronchodilator (L))	0.04	−0.01, 0.08	0.114	61.6	0.005	**-−0.06**	**−0.09, −0.03**	**<0.001**	0	0.471
log (FVC pre-bronchodilator (L))	0.01	−0.03, 0.05	0.551	53.7	0.021	**−0.06**	**−0.08, −0.03**	**<0.001**	0	0.857
log (FVC post-bronchodilator (L))	0.02	−0.03, 0.07	0.408	68.9	<0.001	**−0.06**	**−0.08, −0.03**	**<0.001**	0	0.989
FEV1/FVC ratio pre-bronchodilator	0.02	0.00, 0.03	0.056	0	0.746	−0.01	−0.03, 0.01	0.343	13.5	0.318
FEV1/FVC ratio post-bronchodilator	0.01	−0.01, 0.04	0.217	46.4	0.052	−0.01	−0.03, 0.01	0.550	36.1	0.119

Results of meta-analyses of the effect of principal component scores on respiratory and allergic outcomes. Mean difference, relative risks (RRs), and 95% confidence intervals (95% CI) represent increase in risk per quintile of dietary pattern scores. N = 3206. Bold values indicate *P*-value <0.01.

*All results presented are adjusted for age, sex, smoking status (never, ex-smoker, current), body mass index, age at completion of full-time education, occupation, use of nutritional supplements, and total energy intake (TEI).

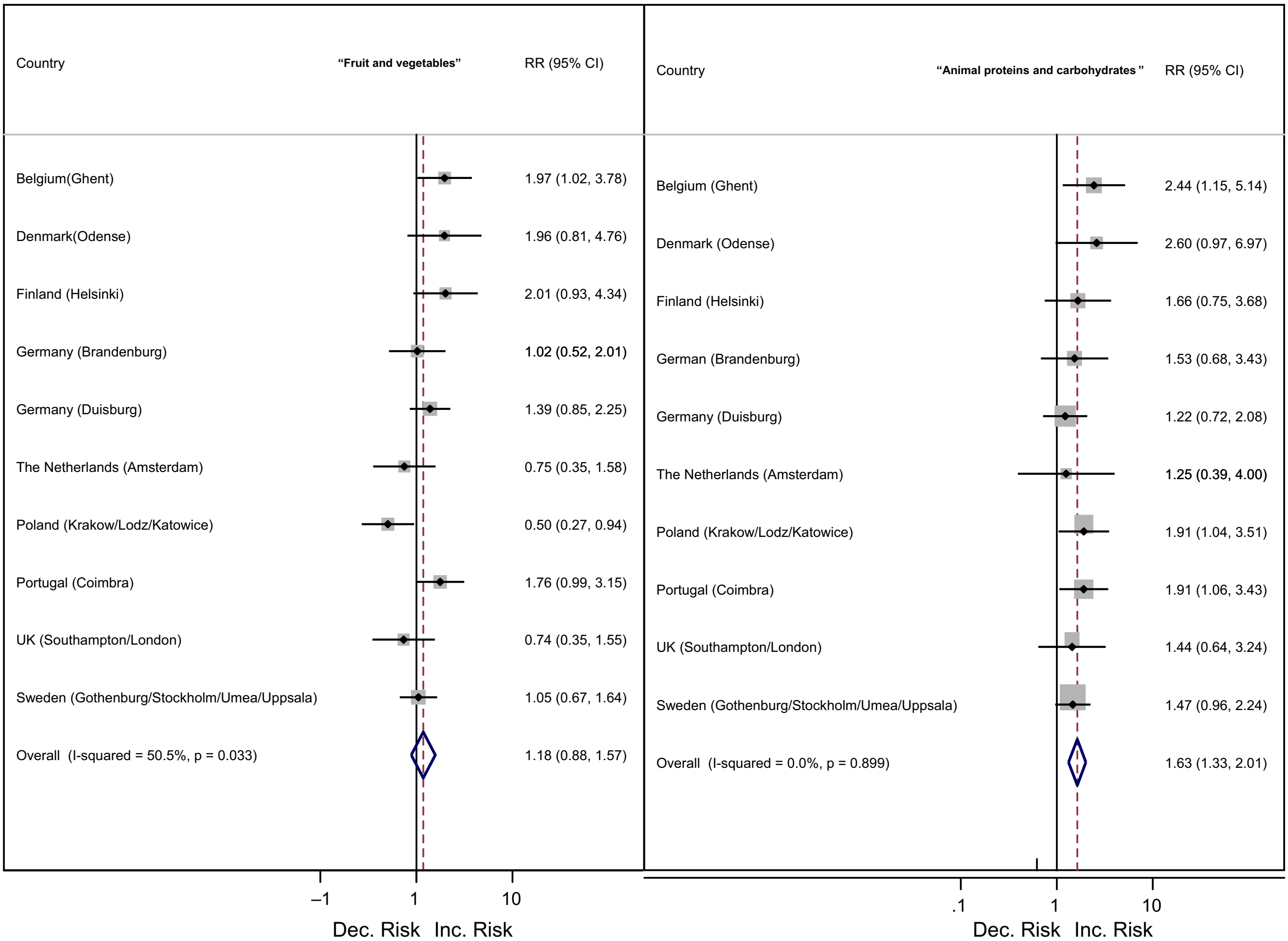

FIGURE 1 Associations between asthma score and "Fruit and Vegetables" and "Animal proteins and Carbohydrates" pattern across 9 countries: results of meta-analyses of the association of asthma score with per quintile dietary pattern scores. RR: Relative risk; 95% CI: 95% Confidence Intervals

1.16-2.44) (Table 2). For lung function, significant associations were seen suggesting increases in risk of FVC < LLN and decreases in pre- and post-bronchodilator mean differences of FEV_1 and FVC, in association with the animal proteins and carbohydrates pattern (Table 3). This was not the case for the FEV_1/FVC ratio. There was no evidence of heterogeneity in the statistically significant associations between the selected respiratory and allergic outcomes with the animal proteins and carbohydrates pattern (*P*-values for heterogeneity were above 0.1).

There was no evidence that a fruit and vegetables pattern was associated with any of the respiratory or allergic outcomes (Table 2). There was no evidence of heterogeneity in the effects associated with an animal protein and carbohydrate dietary pattern, which was consistent across countries. However, there was evidence of heterogeneity in the association of asthma score with the fruit and vegetables pattern (I^2 = 50.5%; *P* = 0.033), and when countries were analyzed separately, increased fruit and vegetables pattern intake was associated with a decreased asthma score in Poland (RR per quintile 0.50; 95% CI 0.27, 0.94) and an increased score in Belgium (RR per quintile 1.97; 95% CI 1.02, 3.78) (Figure 1). There was also evidence of heterogeneity in the associations of FVC and other lung function measures with the fruit and vegetables dietary pattern (Table 3).

4 | DISCUSSION

This multicenter study found cross-sectional associations between asthma, wheeze and allergic sensitization, and a pattern of dietary intake rich in animal proteins and carbohydrates. This pattern was also associated with small decrements of pre- and post-bronchodilator FEV_1 and FVC. There was no strong evidence that a fruit and vegetables pattern was associated with lung function outcomes.

Our findings of an association of animal proteins and carbohydrates pattern with asthma-related symptoms, but not with rhinitis, might suggest that the mechanisms of action might differ across allergic diseases. Our findings are consistent with previous observational studies of 156 035 adult Australian men and women where a meats/cheese dietary pattern was positively associated with asthma (OR 1.18; 95% CI: 1.08-1.28), 54 672 French women[16] where a Western pattern was associated with an increased risk of reporting frequent asthma attacks (OR 1.79; 95% CI: 1.11-3.73), and the Manchester Asthma and Allergy Study[31] where a high adherence to a Western diet pattern was significantly associated with doctor-diagnosed asthma and current asthma at age 8 years (OR 2.19; 95% CI: 1.20-4.01; RR 2.59; 95% CI: 1.15-5.81 respectively) and current asthma at age 11 years (OR 2.20; 95% CI: 1.07-4.51).

Lack of associations between our fruit and vegetables pattern and asthma and related allergic symptoms was consistent with other observational studies of 54 672 French women,[16] and 1453 adults living in Greenwich.[17] Furthermore, our results were consistent with the results of 12008 pregnant women in the Avon Longitudinal Study of Parents and Children[32] where no associations were observed between a "health conscious" (similar to our fruit and vegetables) pattern and asthma, atopy, or eczema.

Diet is strongly socially, environmentally, and culturally patterned with specificities between countries and social groups.[33] Heterogeneity in multicenter studies as observed for the "fruit and vegetable" pattern in Figure 1 could suggest alternative explanations for apparent effects of diet observed in single centers, such as uncontrolled confounding, and would make us cautious about inferring causation and of progressing to a trial.[34] From a methodological point of view, it is possible that some of the heterogeneity observed reflects the wider range of foods included in this category (over 50 fruits and vegetables, while there were less than 30 sources of animal proteins).

In contrast, it is notable that the associations of the animal proteins and carbohydrates dietary patterns with respiratory and allergic symptoms are very consistent between places with a high degree of homogeneity in the effect estimates (Table 2 and the right-hand side of Figure 1).

Our study has several methodological advantages. The analyses we used give us common dietary patterns (weighted sums of standardized food intakes) that we can investigate at every center. A meta-analytic approach to deriving dietary patterns across a number of centers has been investigated once before in nutritional epidemiology[19] but has not otherwise been exploited in this setting. This is partly because FFQ is often specific to a site, making it difficult to pool data. Our study has the advantage of using data from an FFQ that allowed directly comparable data to be collected in different countries. We have shown that the method can be successful in identifying common dietary patterns, as well as providing evidence on the heterogeneity in the effects associated with those patterns. However, given the observational nature of the study, we cannot exclude the possibility of residual confounding.

In conclusion, using meta-PCA, we have demonstrated a consistent association across different countries between a diet with a high intake of animal proteins and carbohydrates and respiratory and allergic outcomes and lung function.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

IB, VGL, RH, and PGB conceived the hypothesis for this analysis. IB wrote the first draft of manuscript. VGL designed the GA^{2}LEN FFQ which was used to collect data on dietary intake in the GA^{2}LEN participants. VGL led the international validation of the GA^{2}LEN FFQ. IB and RH conducted with statistical analyses, with input from VGL and PGB. All co-authors listed in the manuscript contributed to and approved the final version of the manuscript and led the research efforts to collect the data in their participant centers. All authors read and approved the final manuscript.

CONSENT FOR PUBLICATION

All co-authors have read and approved the final version of the manuscript and gave their consent to publish it. Ethics approval and consent to participate. The GA^{2}LEN Survey was approved by the UK's National Research Ethics Service (NRES) No 07/H0604/121. In addition, all participant centers were granted ethical approval to take part in the GA^{2}LEN Follow-up survey, from which this analysis was done. Belgium: Committee for Medical Ethics, University of Ghent. Denmark: Den Videnskabsetiske Komite for Region Syddanmark. Finland: Helsingin Ja Uudenmaan Saira Anhoitopiirin Kuntayhtyma, Eetiset toimukunnat. Germany (both centers): Commission of Ethic, Faculty of Medicine, Heirich Heine Universitat Dusseldorf. Poland: Katowice: Bioethics Commission University of Katowice; Krakow (Commission of Bioethics University of Jagiellonskiego; Lodz (Committee of Bioethics University of Lodz. Portugal: Commission of Ethics for Health, Hospital of the University of Coimbra. Sweden (Joint ethical approval for all four participant centers) Karolinska Institute Ethics Committee. The Netherlands: Medical Ethics Committee, Academic Medical Centre, University of Amsterdam.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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